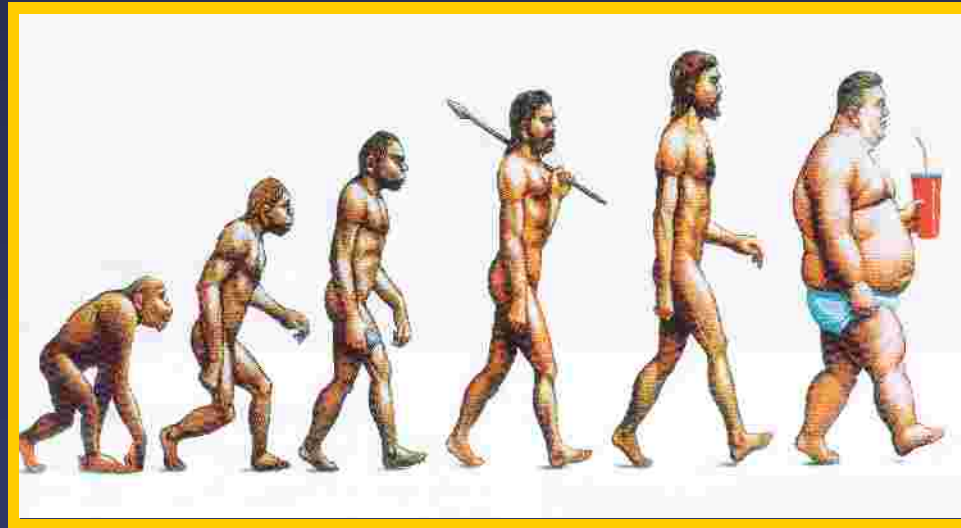# Assessing Cardiovascular Risk
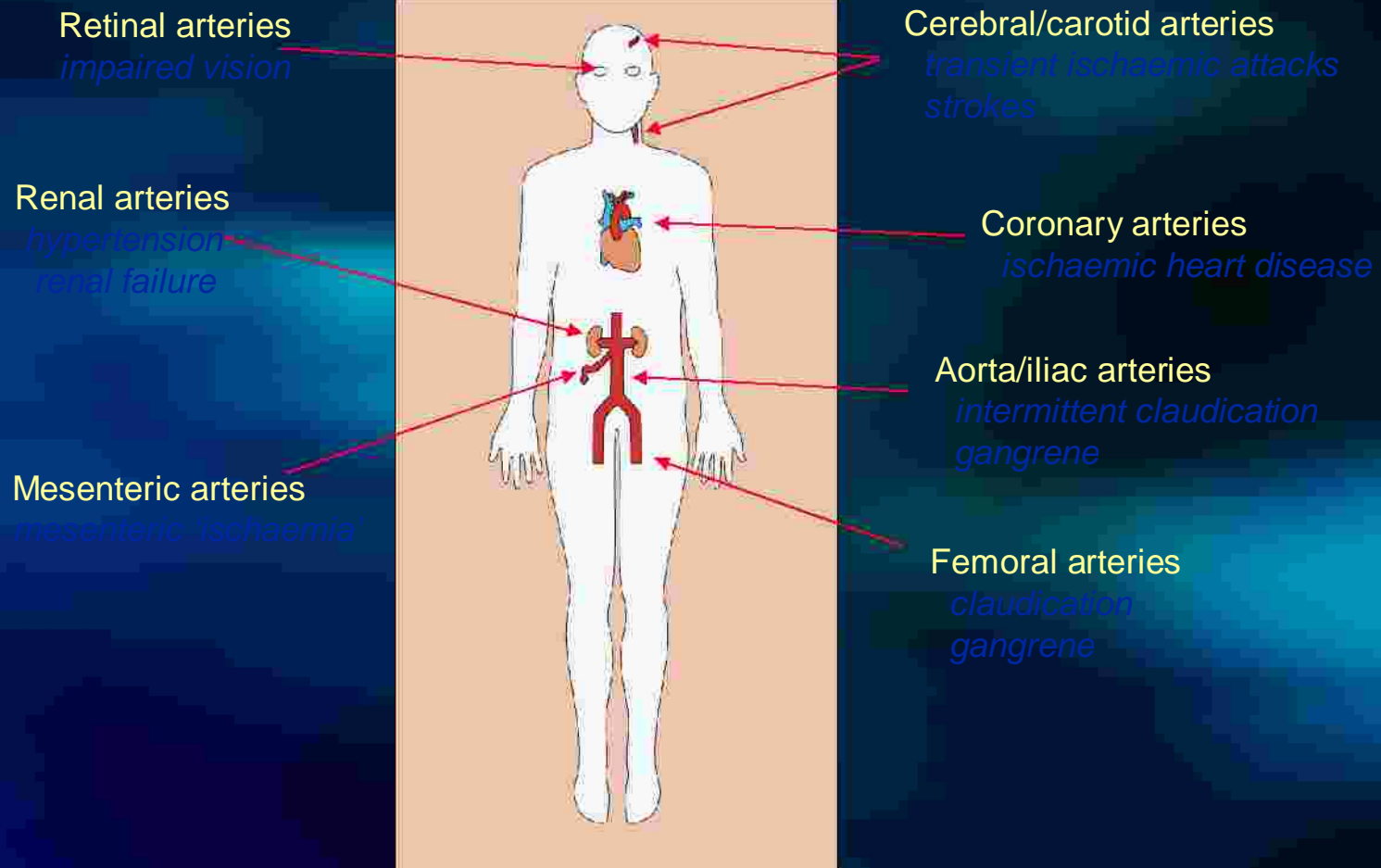
Dr Bernard Prendergast DM FRCP
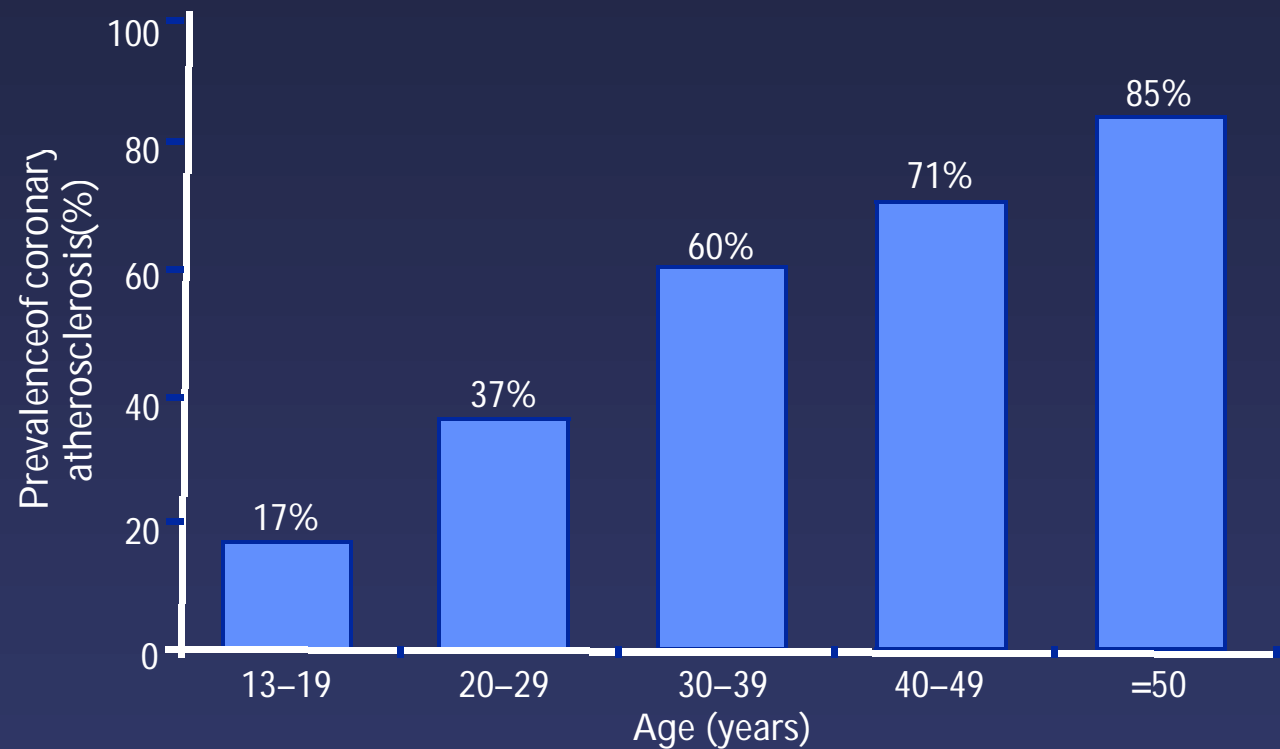
The John Radcliffe Hospital, Oxford, UK

Case History

- 44 year old plumber
- No cardiac symptoms/history
- Non-smoker
- BP 138/78
- FH – é BP, é lipids
- Total cholesterol 5.9mmol/L
- Seeking professional advice

CLINICAL EFFECTS OF ATHEROMA

Retinal arteries
impaired vision

Renal arteries
*hypertension
renal failure*

Mesenteric arteries
mesenteric ischaemia

Cerebral/carotid arteries
*transient ischaemic attacks
strokes*

Coronary arteries
ischaemic heart disease

Aorta/iliac arteries
*intermittent claudication
gangrene*

Femoral arteries
*claudication
gangrene*

Atherosclerosis: When does it begin?

Data from 262 heart transplant donors.
Sites with intimal thickness =0.5 mm were defined as atherosclerotic.

Tuzcu EM, et al.. Circulation. 2001;103:2705-2710.

OUTCOMES IN PATIENTS WITH VASCULAR DISEASE (1)

No room for complacency

- **Myocardial infarction (MI)**
  - 24% of males and 42% of females die within 1 year post-MI
  - 21% of males and 33% of females suffer reinfarction within 6 years and similar numbers are disabled by heart failure
  - 9% of males and 13% of females have a stroke within 6 years
  - In the UK, almost one-third of MI patients are dead at 3 years

- **Transient ischaemic attack (TIA)**
  - Trial data suggest that 5% of untreated patients per year (pa) with TIA's will suffer a permanent stroke
  - Overall mortality is approximately 5% pa with >50% deaths due to coronary artery disease

OUTCOMES IN PATIENTS WITH VASCULAR DISEASE (2)

No room for complacency

- Stroke
  - 29% of stroke patients die within 1 year of initial stroke (these rates are higher in the elderly)
  - >50% of all stroke patients die within 8 years (long-term survival is worse in men)

- Peripheral arterial disease (PAD)
  - Approximately 30% of men with lower extremity occlusive disease will have life-threatening coronary atherosclerosis
  - In men with intermittent claudication (IC) 5-year mortality is 30% and 10-year mortality, 47% (versus 6% and 14% for men with no IC)
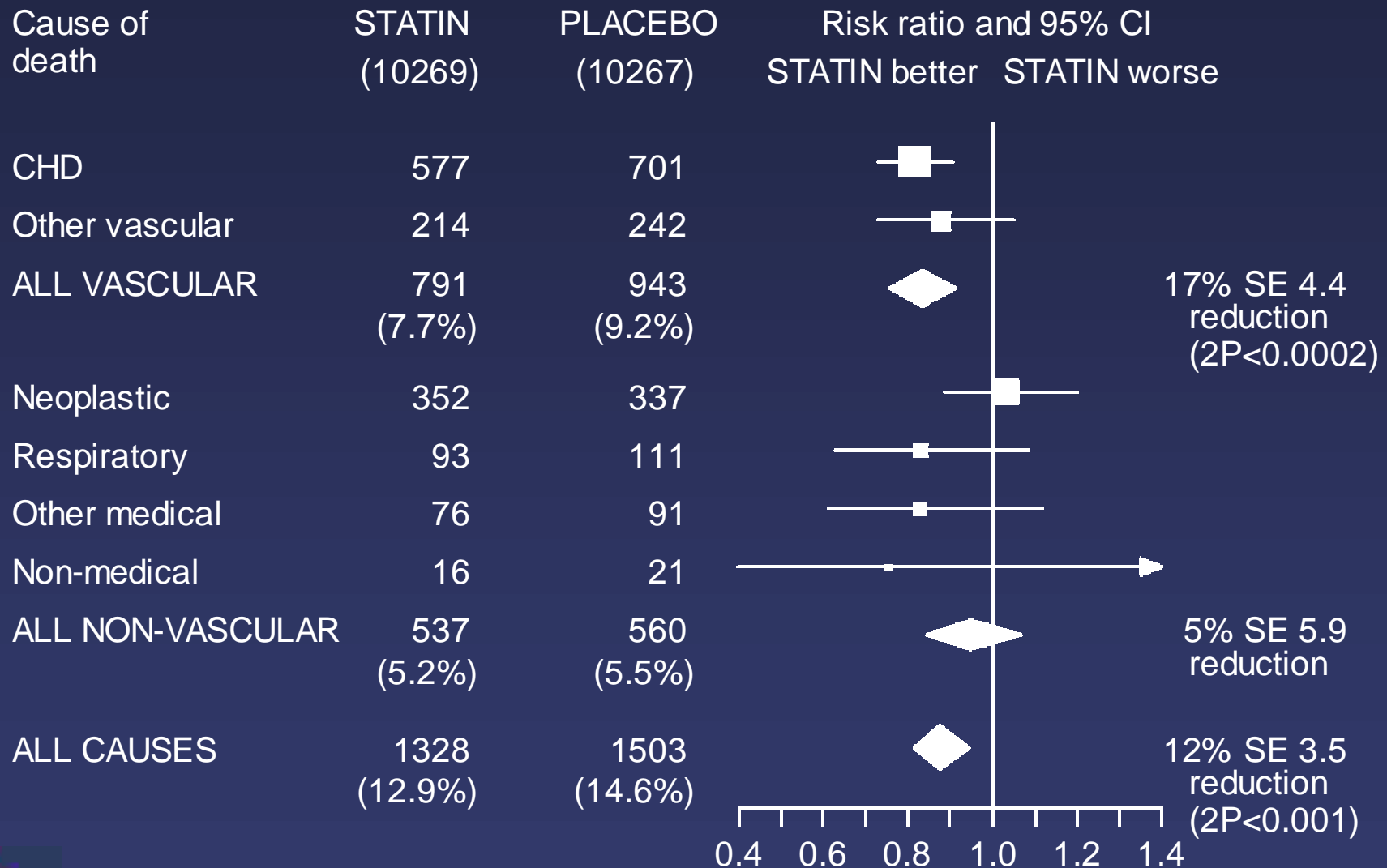
The Heart Protection Study (HPS)

Collins et al, AHA, November 2001

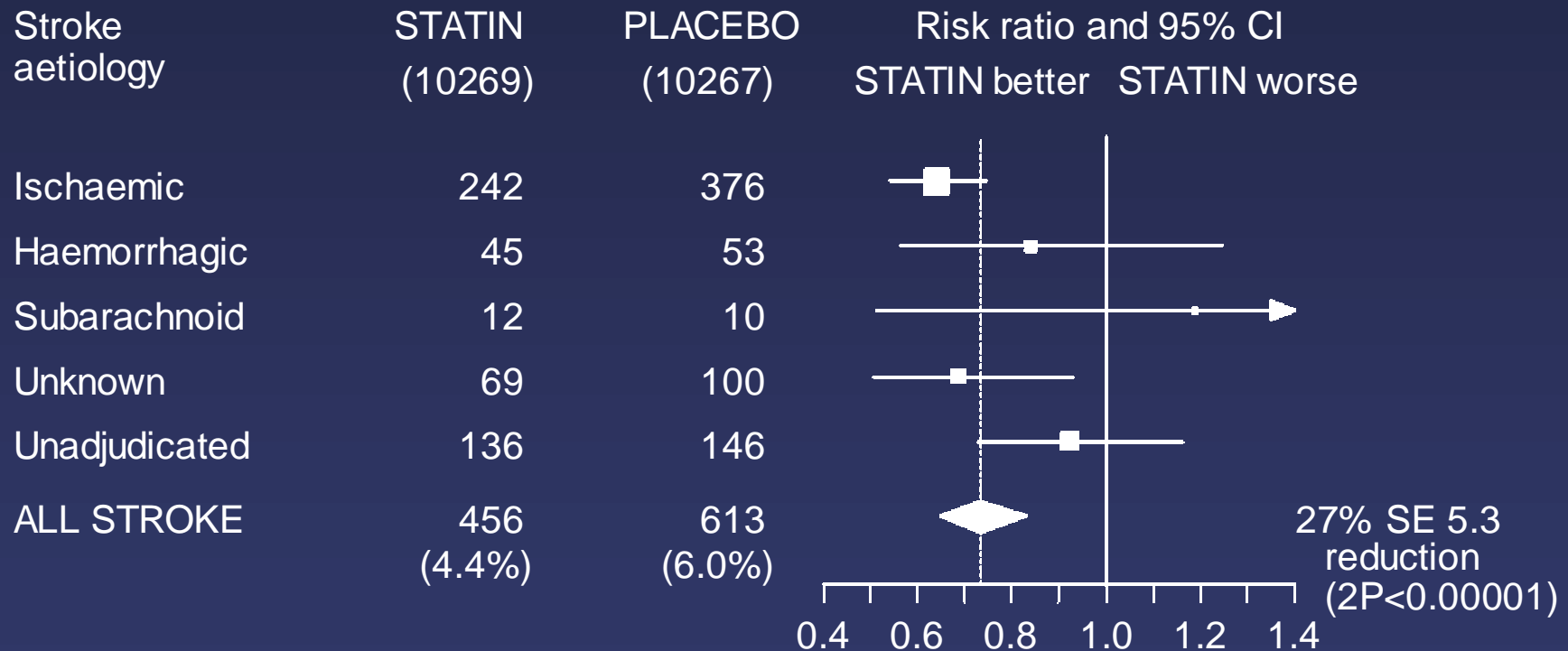- **20,000 volunters, 40-80 years**
- **High CHD risk but no direct evidence of benefit**
- **Average/below average total cholesterol**
  > 3.5mmol/l: 42%, 3.0-3.5mmol/l: 25%, <3.0mmol/l: 33%
- **Included women, >70 yrs, DM, non coronary disease**
- **Simvastatin 40mg od vs. placebo for 5.5 yrs**
- **Subgroups received vitamin C, vitamin E, b-carotene**
- **Standard care: aspirin, b-blockers, nitrates, ACEI**
- **66% compliance, 16% crossover in placebo group**
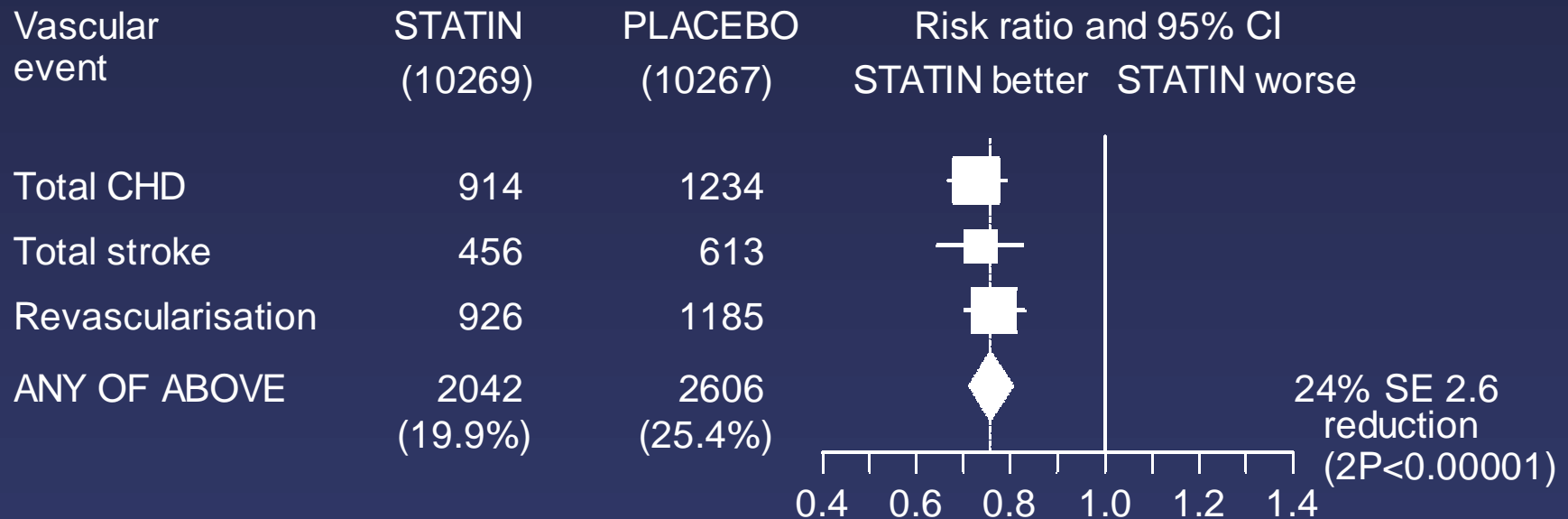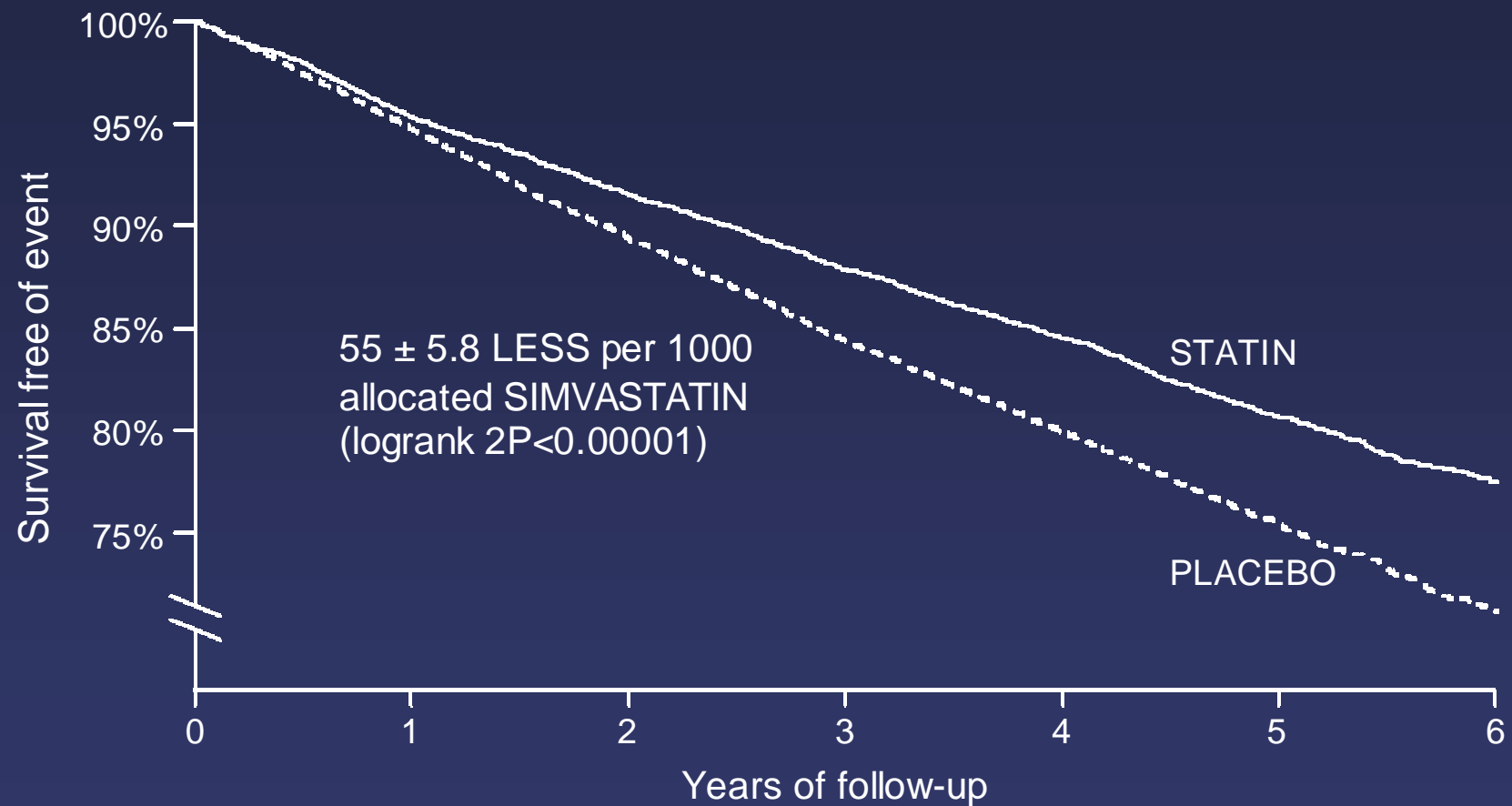
SIMVASTATIN: CAUSE-SPECIFIC MORTALITY

Cause of death	STATIN (10269)	PLACEBO (10267)	Risk ratio and 95% CI
			STATIN better STATIN worse
CHD	577	701	
Other vascular	214	242	
ALL VASCULAR	791 (7.7%)	943 (9.2%)	17% SE 4.4 reduction (2P<0.0002)
Neoplastic	352	337	
Respiratory	93	111	
Other medical	76	91	
Non-medical	16	21	
ALL NON-VASCULAR	537 (5.2%)	560 (5.5%)	5% SE 5.9 reduction
ALL CAUSES	1328 (12.9%)	1503 (14.6%)	12% SE 3.5 reduction (2P<0.001)

0.4   0.6   0.8   1.0   1.2   1.4

hps

SIMVASTATIN: STROKE by AETIOLOGY

Stroke aetiology	STATIN (10269)	PLACEBO (10267)	Risk ratio and 95% CI STATIN better STATIN worse
Ischaemic	242	376	
Haemorrhagic	45	53	
Subarachnoid	12	10	
Unknown	69	100	
Unadjudicated	136	146	
ALL STROKE	456 (4.4%)	613 (6.0%)	27% SE 5.3 reduction (2P<0.00001)

0.4   0.6   0.8   1.0   1.2   1.4

SIMVASTATIN: MAJOR VASCULAR EVENTS

Vascular event	STATIN (10269)	PLACEBO (10267)	Risk ratio and 95% CI
			STATIN better STATIN worse
Total CHD	914	1234	
Total stroke	456	613	
Revascularisation	926	1185	
ANY OF ABOVE	2042 (19.9%)	2606 (25.4%)	24% SE 2.6 reduction (2P<0.00001)

0.4   0.6   0.8   1.0   1.2   1.4

SIMVASTATIN: VASCULAR EVENT by AGE & SEX

Baseline feature	STATIN (10269)	PLACEBO (10267)	Risk ratio and 95% CI STATIN better STATIN worse	
Age group (years)				
< 65	838	1093		
65 - 69	516	677		
70-74	550	628		$\text{Het } c^2_3 = 4.4$
³ 75	138	208		
Sex				
Male	1676	2148		
Female	366	458		$\text{Het } c^2_1 = 0.4$
ALL PATIENTS	2042 (19.9%)	2606 (25.4%)		24%SE 2.6 reduction (2P<0.00001)

0.4   0.6   0.8   1.0   1.2   1.4
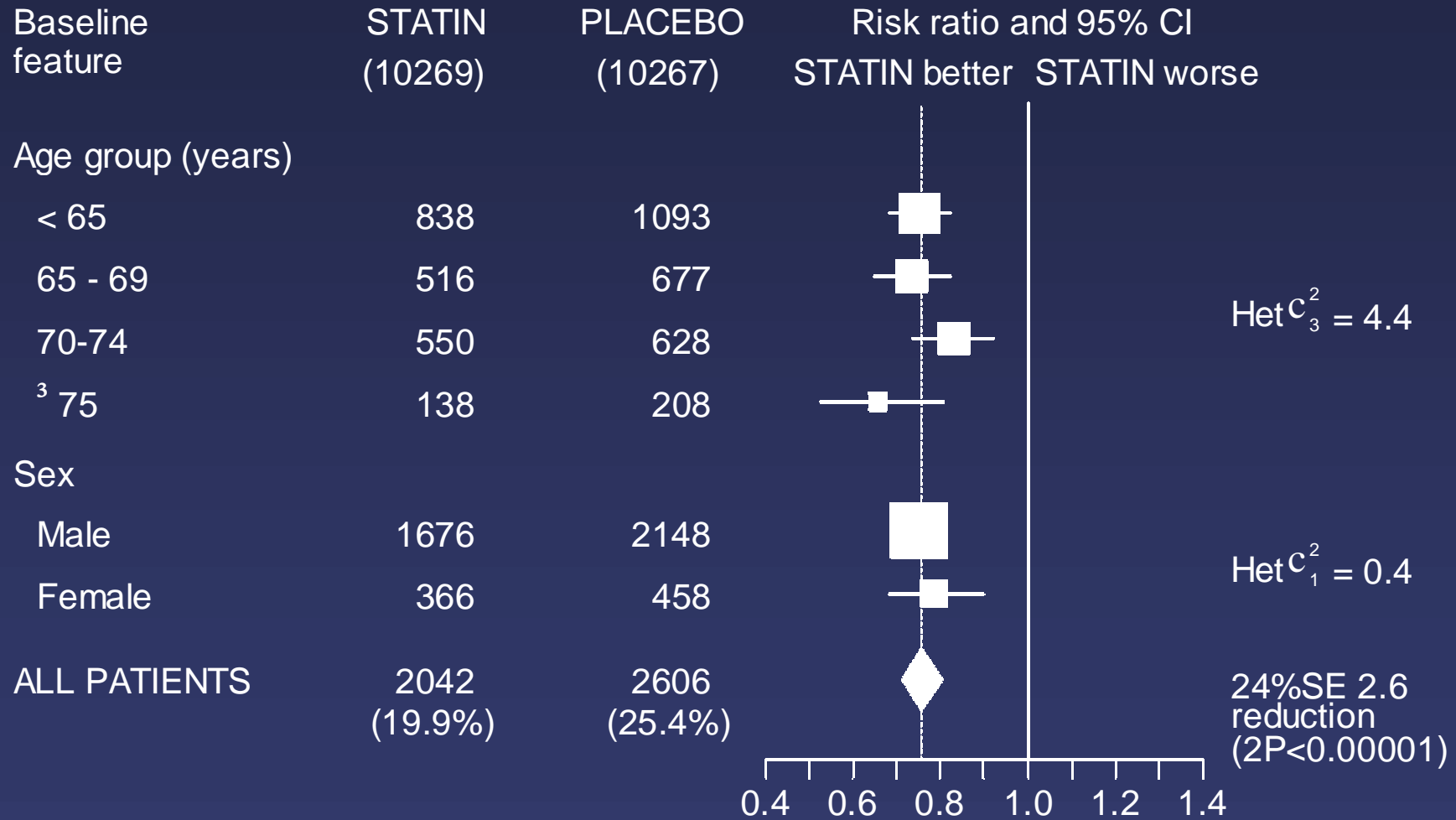
SIMVASTATIN: VASCULAR EVENT by PRIOR LIPID LEVELS

Baseline feature	STATIN (10269)	PLACEBO (10267)	Risk ratio and 95% CI	
			STATIN better	STATIN worse
LDL (mmol/l)				
< 3.0 (116 mg/dl)	602	761		
3.0 < 3.5	483	655		Het $\chi^2_2 = 3.0$
3.5 (135 mg/dl)	957	1190		
Total cholesterol (mmol/l)				
<5.0 (193 mg/dl)	361	476		
5.0 < 6.0	746	965		Het $\chi^2_2 = 0.5$
6.0 (232 mg/dl)	935	1165		
ALL PATIENTS	2042 (19.9%)	2606 (25.4%)		24%SE 2.6 reduction (2P<0.00001)

0.4 0.6 0.8 1.0 1.2 1.4
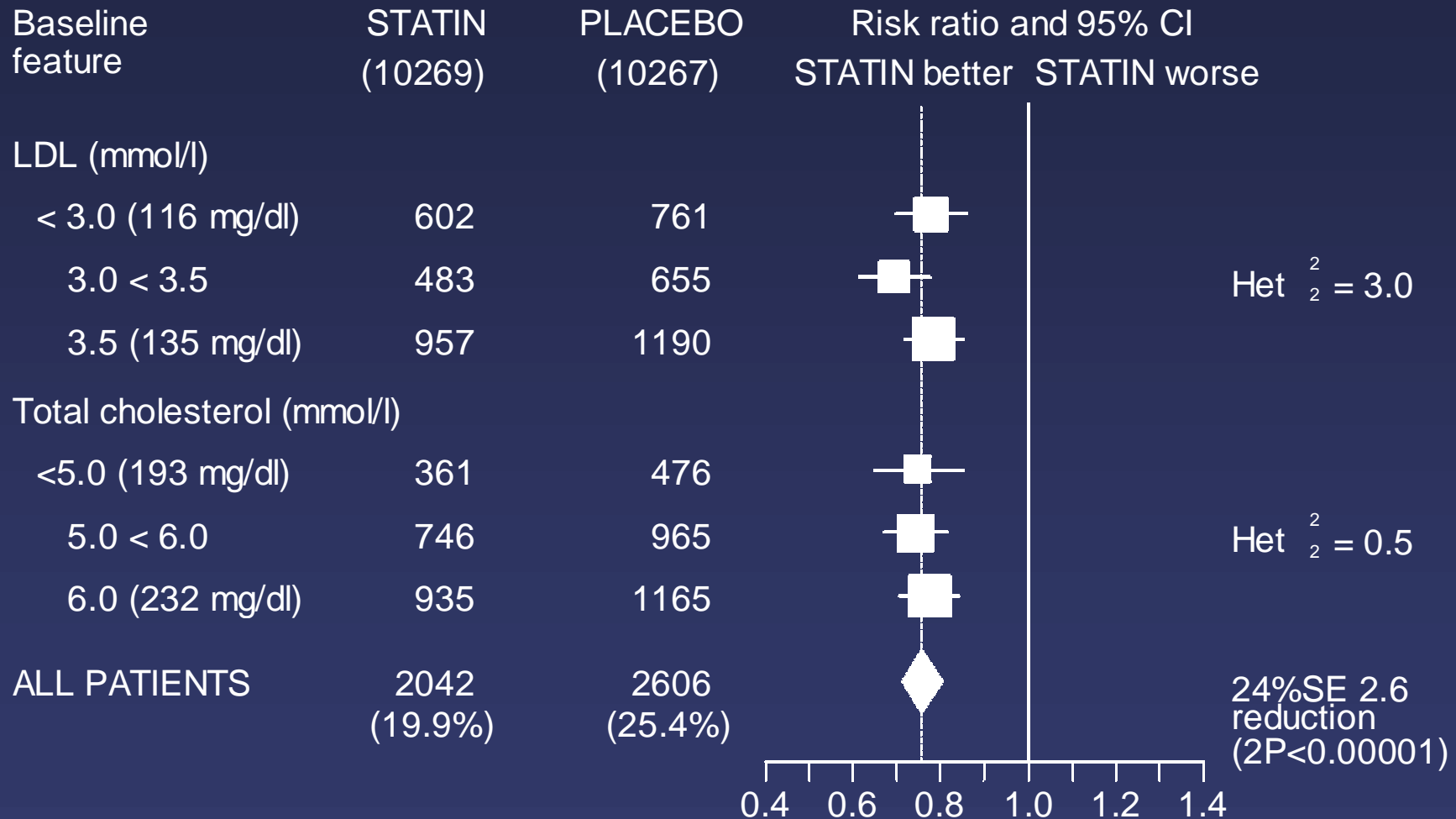
SIMVASTATIN: Safety monitoring

Blood enzymes (x upper limit of normal)	STATIN (10,269)	PLACEBO (10,267)
Liver: ALT>3xULN	77 (0.8%)	65 (0.6%)
Muscle: CK >10xULN	9 (0.09%)	5 (0.05%)
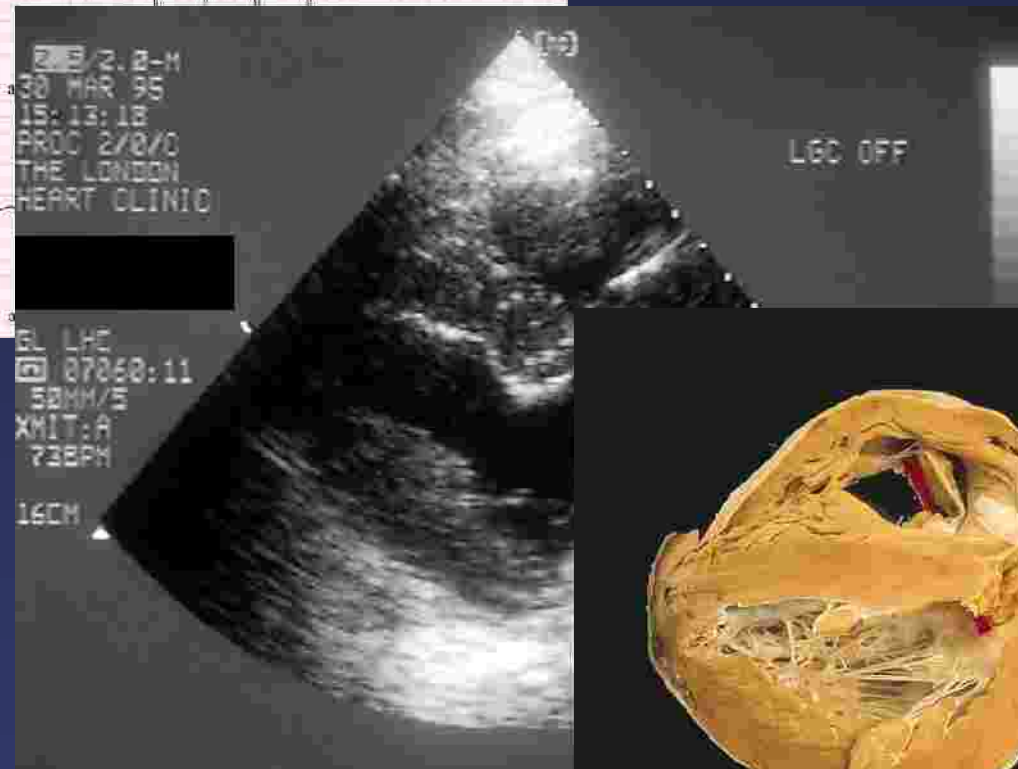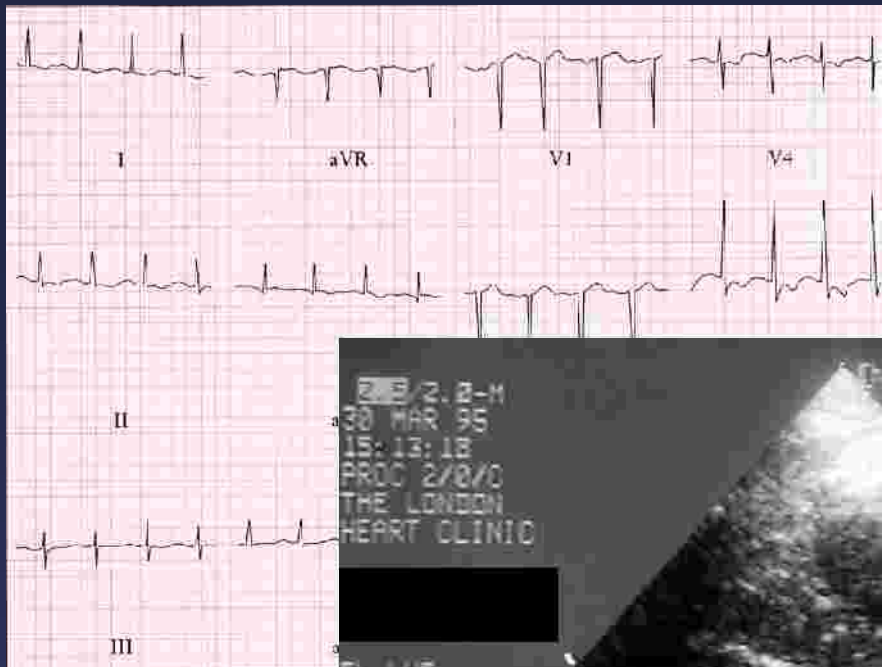
JOINT NATIONAL COMMITTEE CLASSIFICATION OF HYPERTENSION

Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	<130	<85
High normal	130 — 139	85 — 89
Hypertension		
Stage 1 (mild)	140 — 159	90 — 99
Stage 2 (moderate)	160 — 179	100 — 109
Stage 3 (severe)	180 — 209	110 — 119
Stage 4 (very severe)	≥210	≥120

The British Hypertension Society recommendations for combining Blood Pressure Lowering drugs

BHS

Younger (e.g.<55yr) and Non-Black

Older (e.g.≥55yr) or Black

Step 1 — A (or B*) — C or D

Step 2 — A (or B*) + C or D

Step 3 — A (or B*) + C + D

Step 4 Resistant Hypertension — Add: either α-blocker or spironolactone or other diuretic
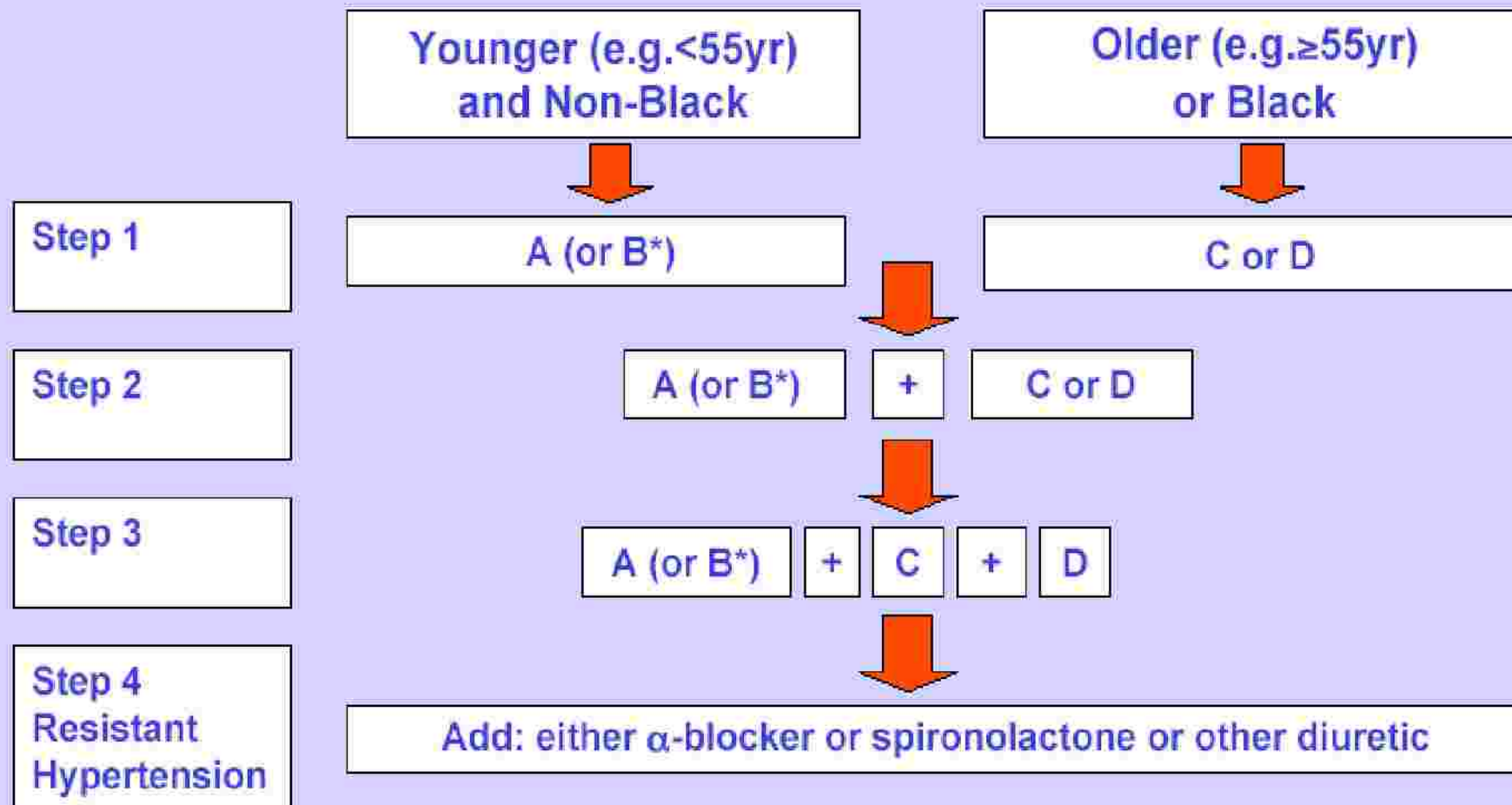
A: AIIA or ACE inhibitor   B: β - blocker
C: Calcium channel blocker   D: Diuretic (thiazide)

* Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies

Heart Outcomes Prevention Evaluation Study

A large, double blind, randomised trial of ramipril and vitamin E in patients at high risk for cardiovascular events

Primary Outcome - Death from cardiovascular causes, MI and stroke
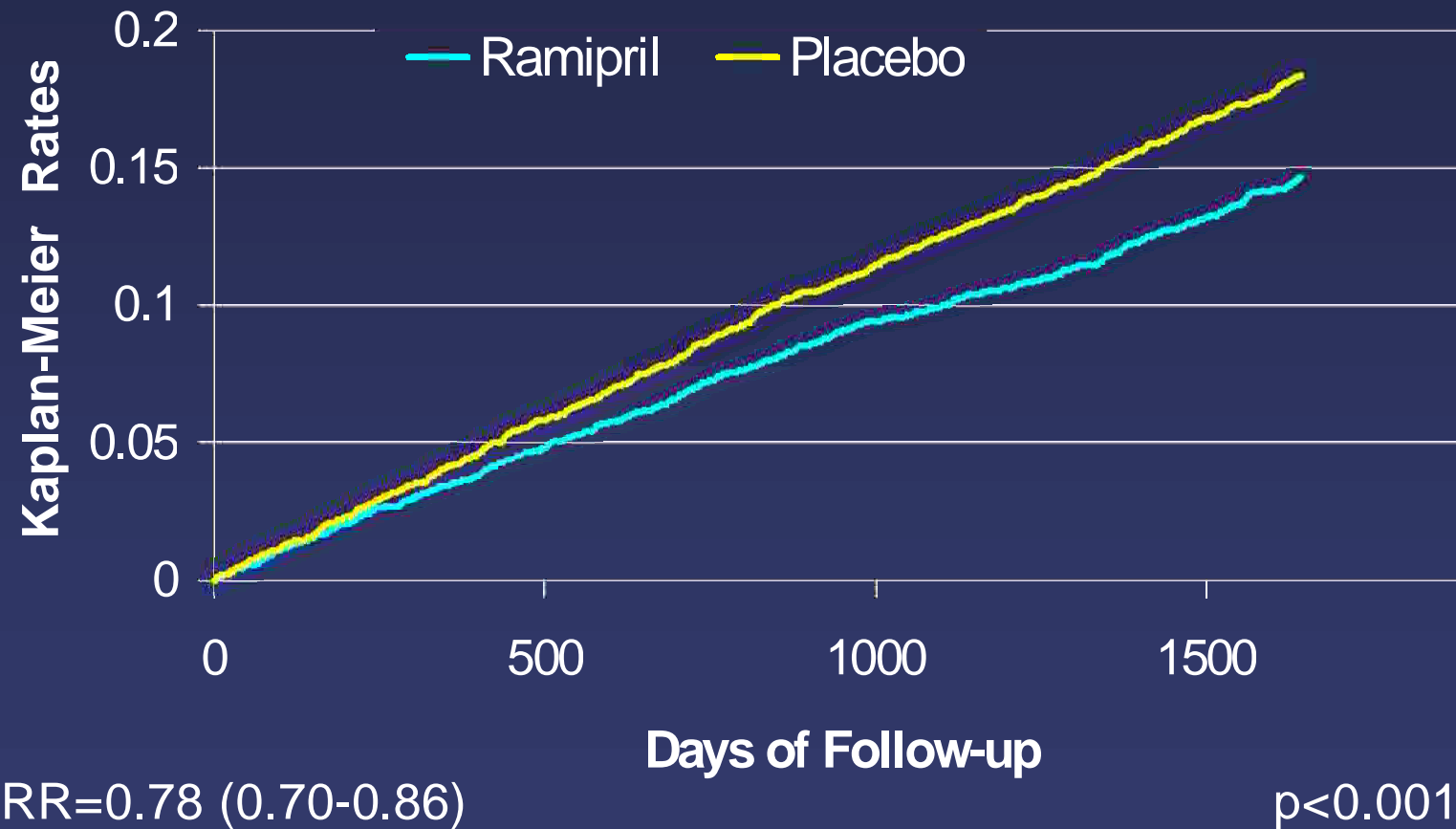
DIABETES AND HIGH VASCULAR RISK

TYPE 2 DIABETES MELLITUS

↑Platelet adhesiveness Coagulation

↑Plasminogen activator inhibitor type 1

↑Oxidised LDL

↑VLDL ↓HDL

↑Oxidative stress

Dysfibrinolysis Hypercoagulation

Endothelial dysfunction

Vascular damage Smooth muscle cell proliferation

ATHEROSCLEROSIS
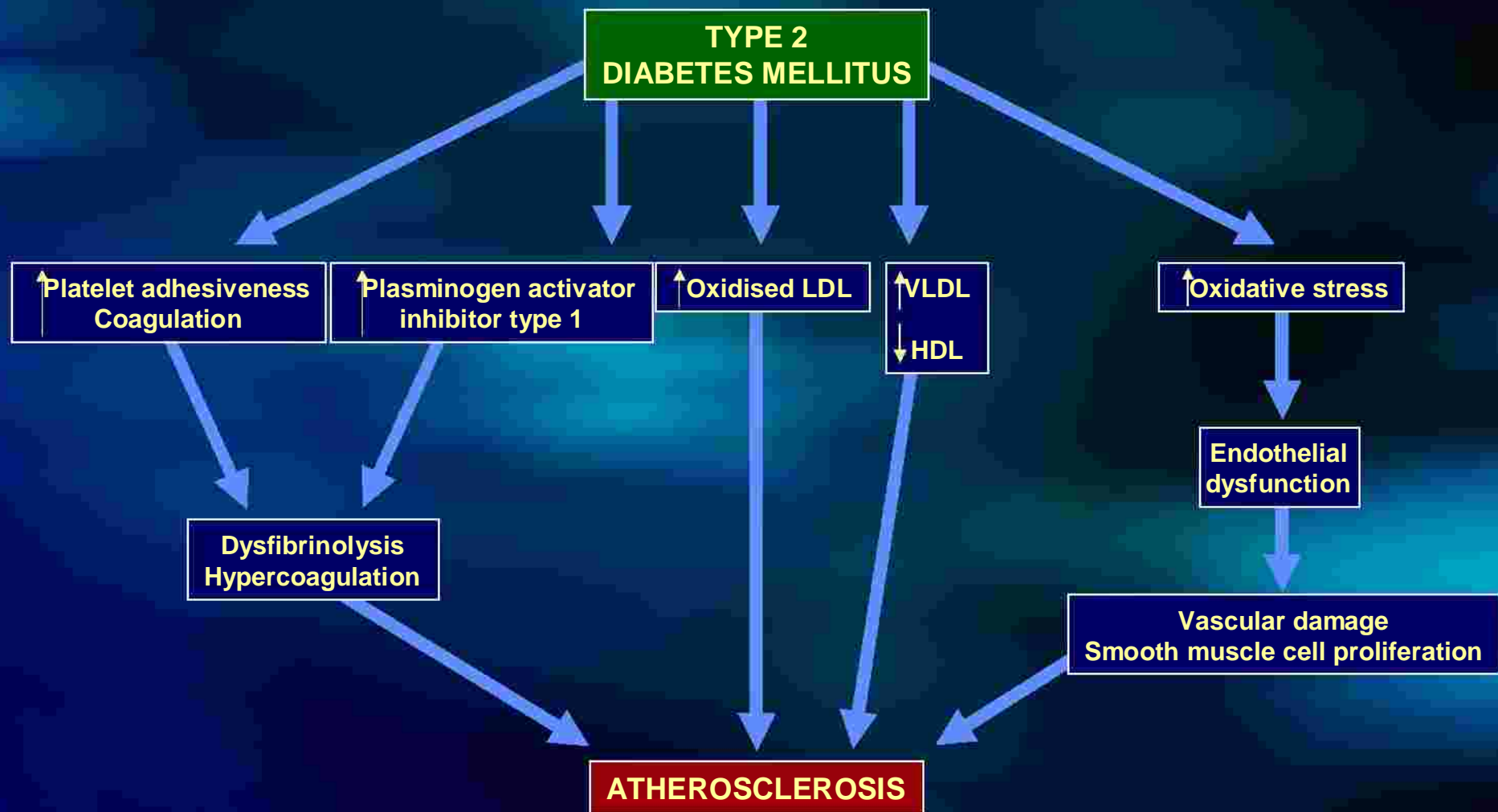
Type II diabetics are a high cardiovascular risk group

7-year incidence of cardiovascular events (%)

Legend:
- Nondiabetic subjects
- Subjects with type 2 diabetes

Categories:
- Myocardial infarction
- Stroke
- Cardiovascular deaths

(with -MI and +MI bars for each)
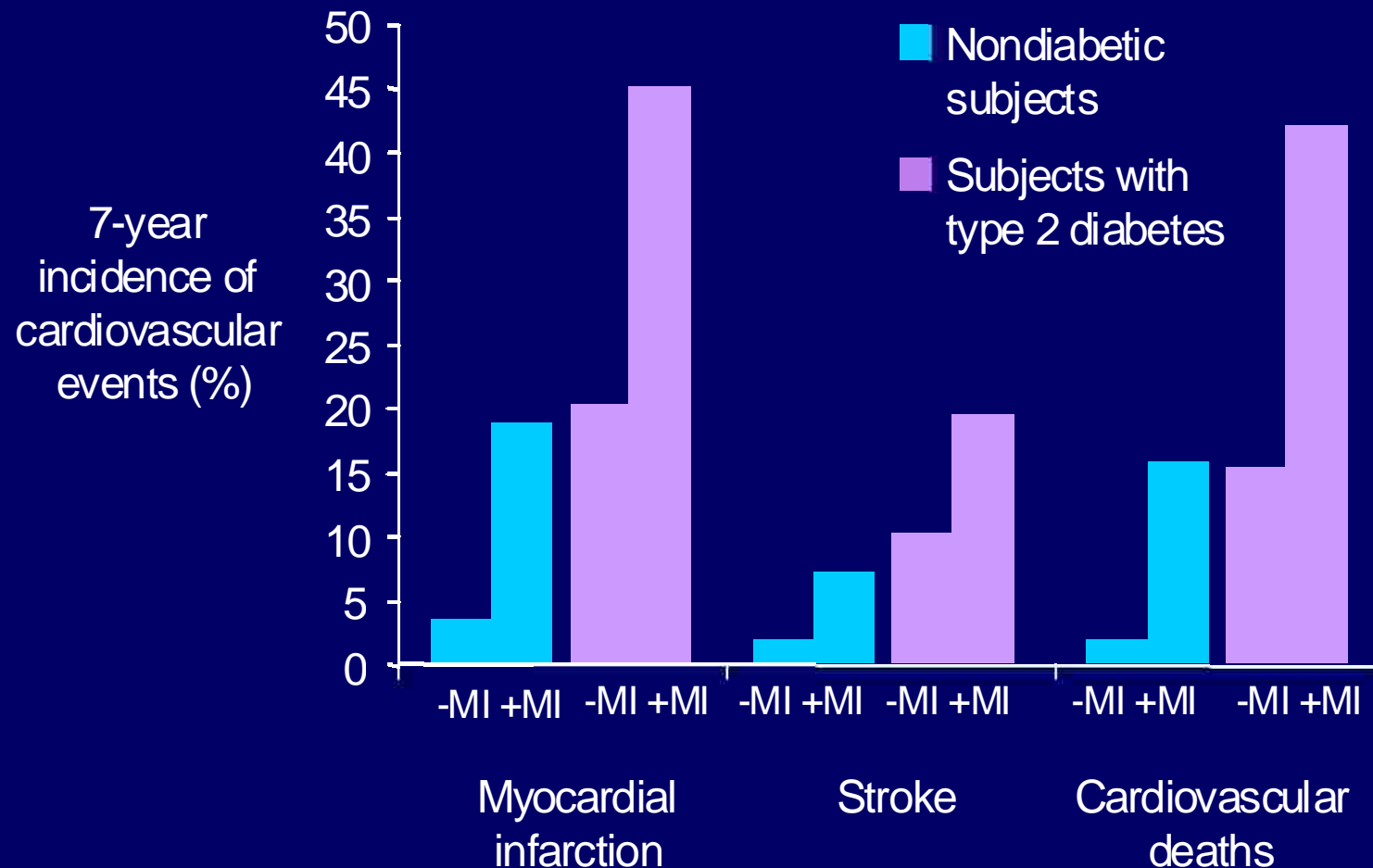
- MI = no prior myocardial infarction; + MI = prior myocardial infarction.
Haffner SM et al. *N Engl J Med.* 1998;339:229-234.
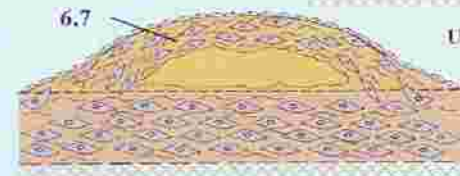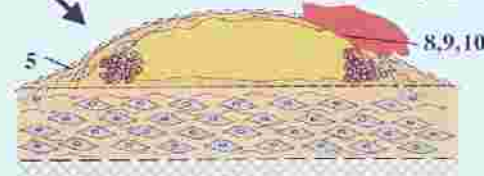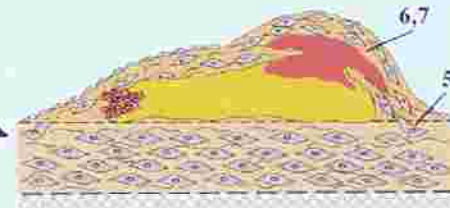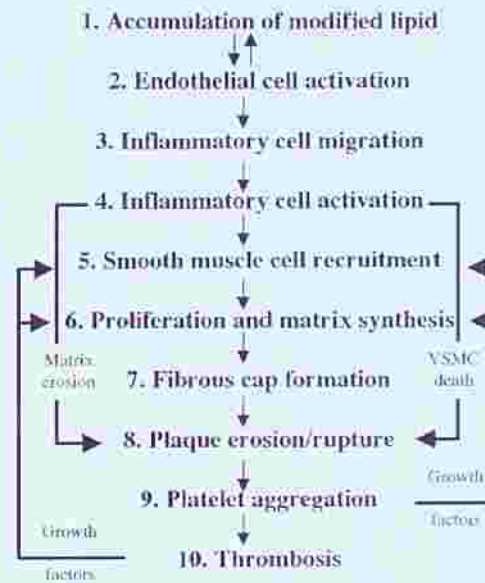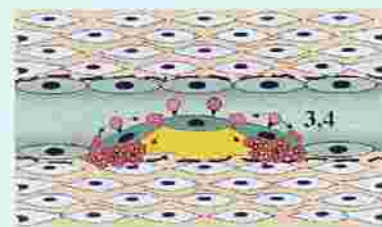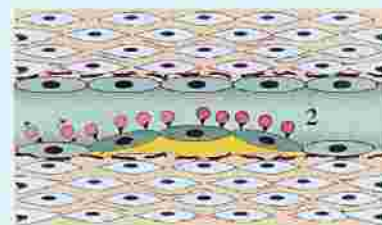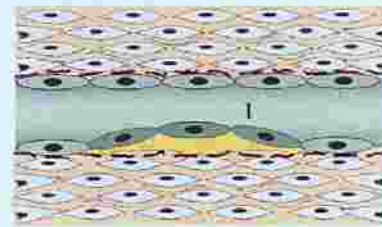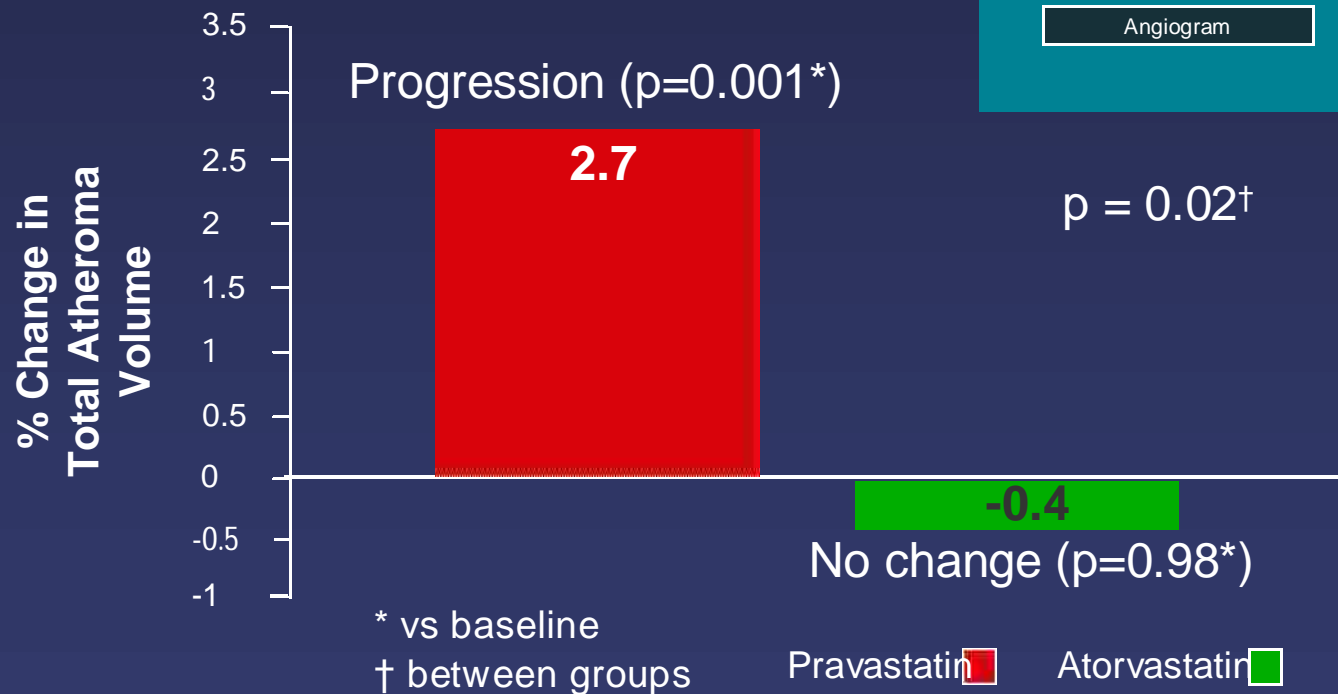
Disease Reversal – Fact or Fantasy?

REVERSAL: Why was IVUS used?

Angiogram | IVUS Image

Progression (p=0.001*)

2.7

$p = 0.02^{\dagger}$

-0.4

No change (p=0.98*)

% Change in Total Atheroma Volume

3.5
3
2.5
2
1.5
1
0.5
0
-0.5
-1

* vs baseline
† between groups

Pravastatin ■   Atorvastatin ■

Nissen SE et al. JAMA 2004; 291(9)1071-1080
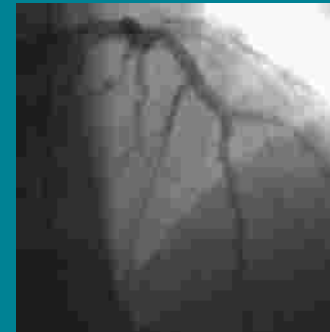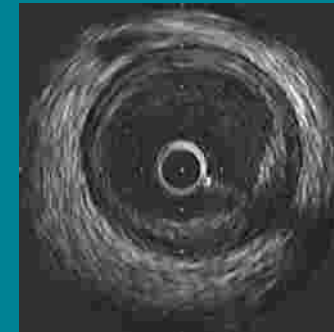
Case History

- 43 year old female
- Non-smoker
- BP 140/70
- Normal glucose
- Total cholesterol 4.2 mmol/L
- Chest pain at local bingo hall
- Evolving anterior STEMI

MIRACL

- Effects of early-initiated atorvastatin 80mg after an acute coronary syndrome on death and recurrent ischaemic events

- Randomised, double-blind, placebo-controlled trial

- Patients were assigned to atorvastatin 80mg or placebo 24–96 hours after hospital admission for ACS
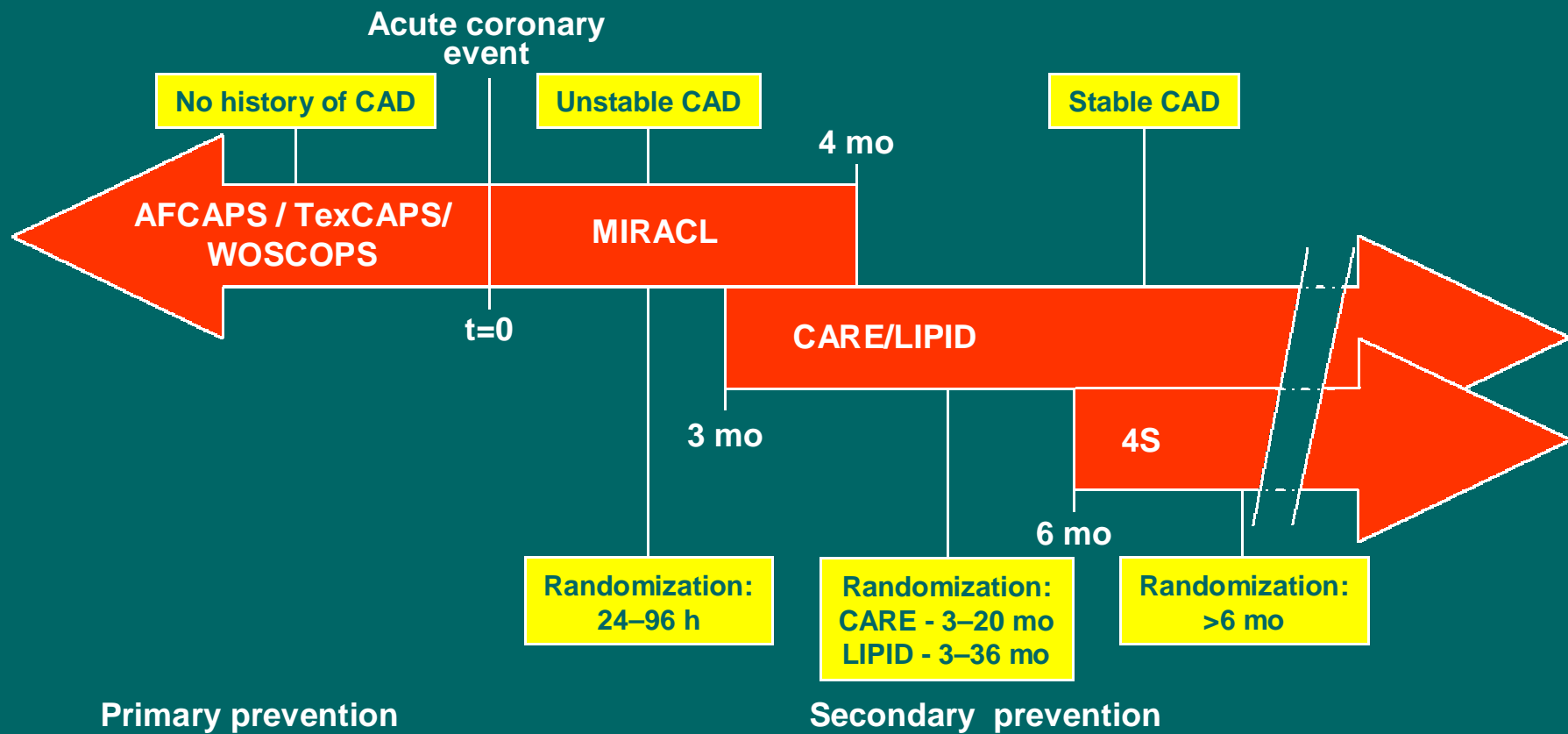
Schwartz GG et al. JAMA 2001; **285** (13): 1711-1718

Primary endpoint*

Cumulative incidence (%) vs Time since randomisation (weeks)

Placebo 17.4%

Atorvastatin 14.8%

16% Relative Risk Reduction

16% RRR
HR 0.84 (0.70-0.99)
P=0.048
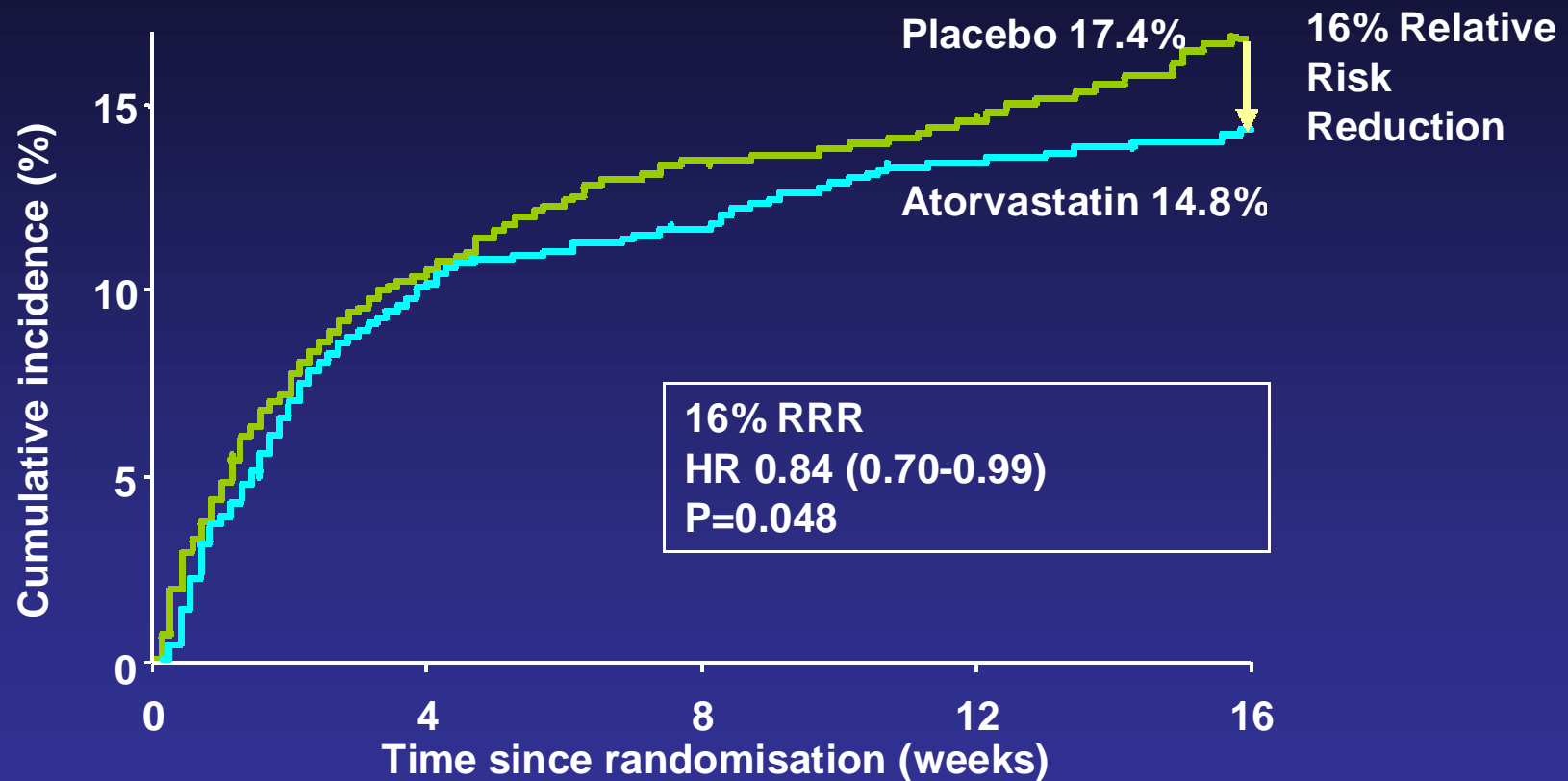
* Primary endpoint=death, non-fatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischaemia with objective evidence and requiring emergency rehospitalisation

Conclusion: Comparison with other trials
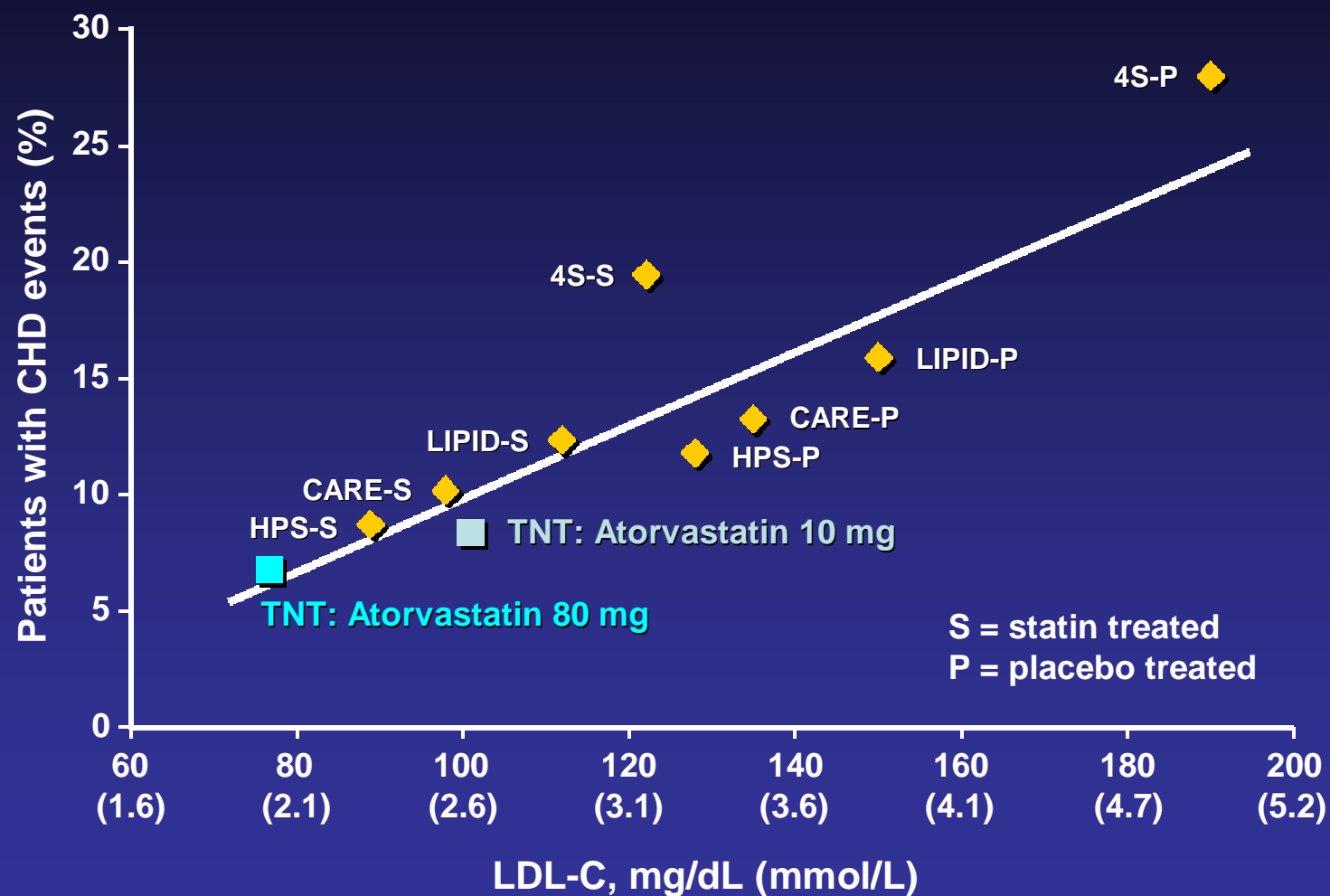
Acute coronary event

No history of CAD

Unstable CAD

Stable CAD

4 mo

AFCAPS / TexCAPS/ WOSCOPS

MIRACL

t=0

CARE/LIPID

3 mo

4S

6 mo

Randomization: 24–96 h

Randomization: CARE - 3–20 mo LIPID - 3–36 mo

Randomization: >6 mo

Primary prevention

Secondary prevention

*Schwartz GG et al. Am J Cardiol 1998;**81**:578–581.*

Cholesterol – How low is low?

National Service Framework(NSF) for Cardiology

    cholesterol < 5 mmol/lt or a 25% reduction whichever greater

    LDL   < 3 mmol/lt or a 30% reduction whichever greater

British Joint Society Guidelines

    cholesterol < 4 mmol/lt or a 25% reduction

    LDL   < 2 mmol/lt or a 30% reduction

Lipid modification

Implementing NICE guidance

2008

NICE clinical guideline 67
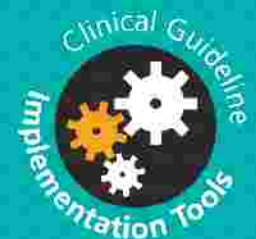
Primary prevention: identifying high risk

Adopt a systematic strategy

Identify people aged 40–74 without diabetes or known CVD

Estimate risk using factors already recorded in primary care electronic medical records

Prioritise people with estimated 10-year risk = 20%

Discuss risk assessment, including option to decline

Primary prevention:
full formal risk assessment

Use Framingham 1991 10-year risk equations to assess CVD risk:

CVD risk = 10-year risk of fatal and non-fatal stroke, including transient ischaemic attack + 10-year risk of coronary heart disease (CHD)

Primary prevention:
lipid modification therapy

Before offering lipid modification therapy consider all other modifiable CVD risk factors and optimise if possible:

- smoking status
- BMI/obesity
- alcohol intake
- cholesterol
- blood pressure

Primary prevention: statin therapy

- Offer statin therapy for adults who have a 20% or greater 10-year risk of developing CVD
- Initiate treatment with simvastatin 40 mg
- If simvastatin 40 mg is contraindicated, offer a lower dose or alternative preparation (such as pravastatin)
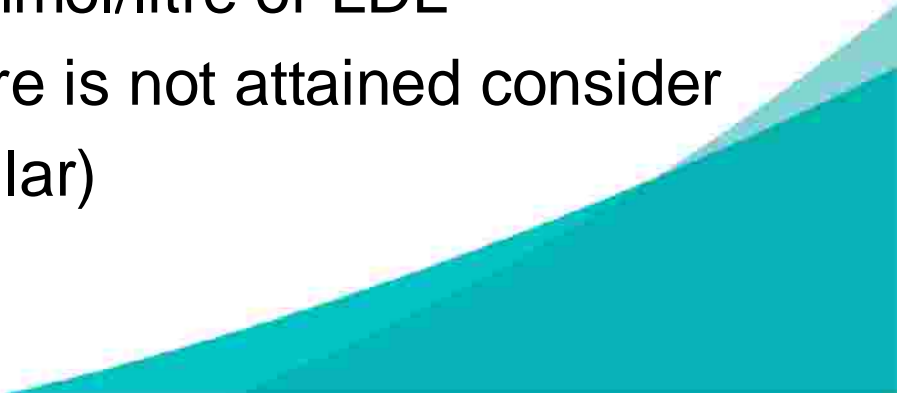- A target for total or LDL cholesterol is not recommended

Secondary prevention: statin therapy

- Offer statin therapy to adults with clinical evidence of CVD

- Offer higher intensity statin to people with acute coronary syndrome, taking into account:
  - the patient's informed preference
  - comorbidities
  - multiple drug therapy, and
  - the benefits and risks of treatment

Secondary prevention:
statin therapy *continued*

- Treatment should be initiated with simvastatin 40 mg

- If simvastatin 40 mg is contraindicated, offer a lower dose or alternative preparation (such as pravastatin)

- If total cholesterol of < 4 mmol/litre or LDL cholesterol of < 2 mmol/litre is not attained consider simvastatin 80 mg (or similar)

Benefits and savings

When fully implemented the guideline could lead to:

- 14,800 CVD events being avoided nationally per year
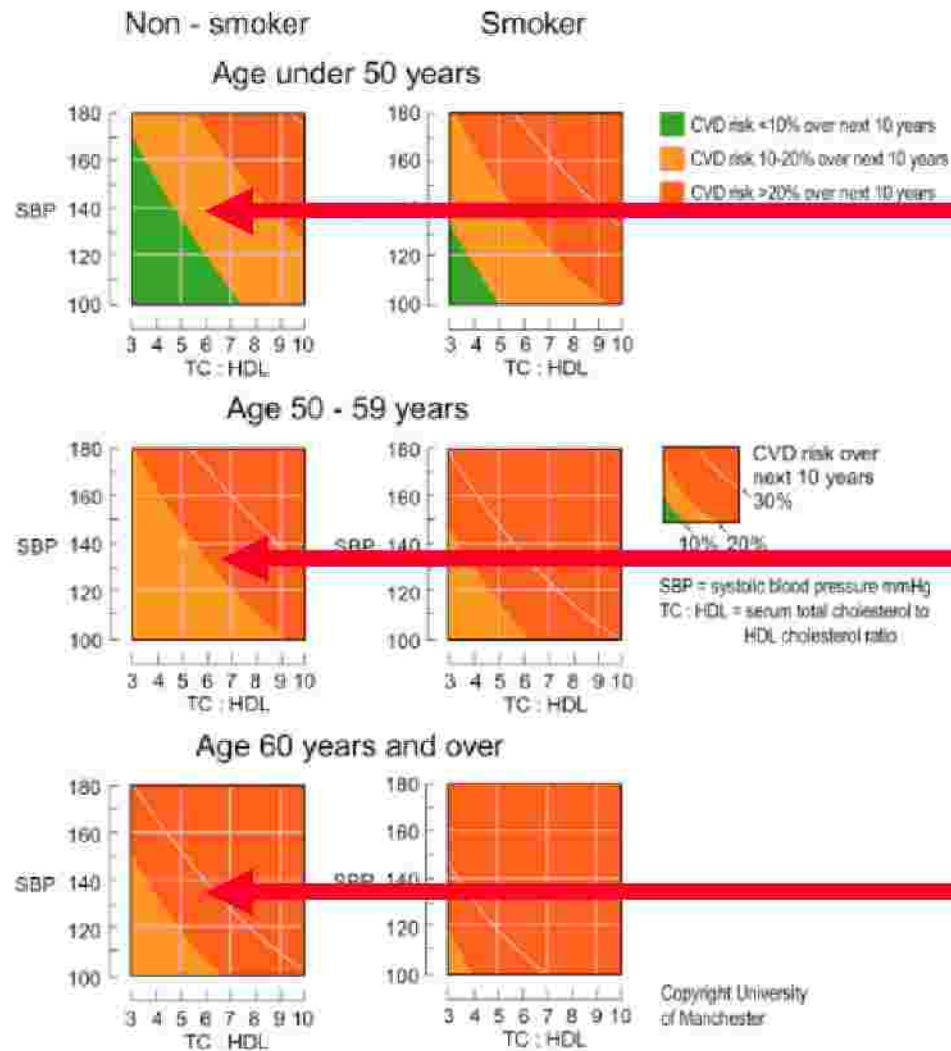- at least £50 million saved annually

Case History

- 44 year old plumber
- No cardiac symptoms/history
- Non-smoker
- BP 138/78
- FH – é BP, é lipids
- Total cholesterol 5.9mmol/L
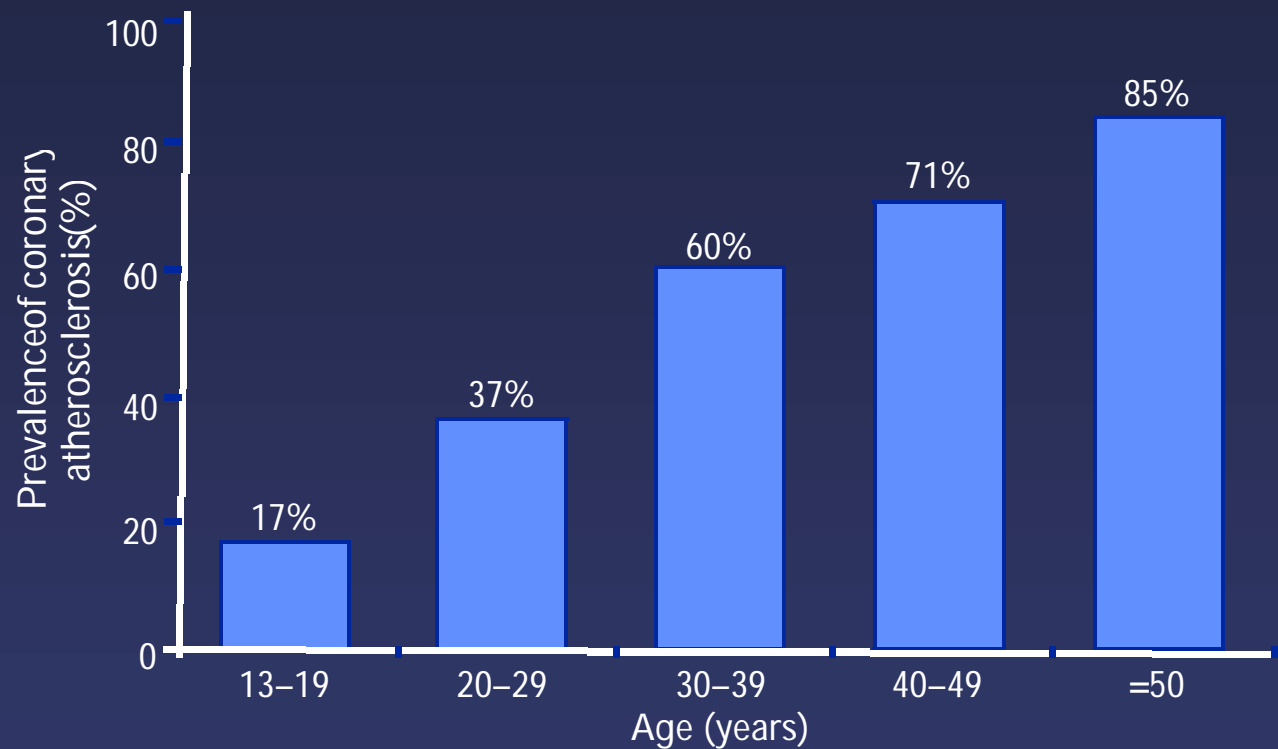- Seeking professional advice

Nondiabetic Men

2008

2014

2024